Aqueous Polymeric Coatings for Pharmaceutical Dosage Forms

Third Edition

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informa
healthcare
New York London

Informa Healthcare USA, Inc.
52 Vanderbilt Avenue
New York, NY 10017

Printed in the United States of America on acid-free paper
10 9 8 7 6 5 4 3 2 1

International Standard Book Number-10: 0-8493-8789-2 (hardcover : alk. paper)
International Standard Book Number-13: 978-0-8493-8789-0 (hardcover : alk. paper)

Library of Congress Cataloging-in-Publication Data

Aqueous polymeric coatings for pharmaceutical dosage forms / edited by James W. McGinity, Linda A. Felton. — 3rd ed.
p. ; cm. (Drugs and the pharmaceutical sciences ; v. 176)
Includes bibliographical references and index.
ISBN-13: 978-0-8493-8789-0 (hardcover : alk. paper)
ISBN-10: 0-8493-8789-2 (hardcover : alk. paper)
1. Drugs — Coatings. 2. Aqueous polymeric coatings in pharmaceutical technology. I. McGinity, James W. II. Felton, Linda A. III. Series.
[DNLM: 1. Dosage Forms. 2. Polymers — therapeutic use. W1 DR893B v.176 2008 / QV 785 A656 2008]
RS199.C63A67 2008
615'.19 — dc22 2007033150

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Adhesion of Polymeric Films

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INTRODUCTION

Adhesion between a polymer and the surface of a solid is a major prerequisite for the film coating of pharmaceutical dosage forms (1–3). Loss of adhesion may lead to an accumulation of moisture at the film–tablet interface, potentially affecting the stability of drugs susceptible to hydrolytic degradation (4). Poor adhesion may also compromise the mechanical protection that the coating provides to the substrate (5). In addition, experiments on adhesion are useful to the pharmaceutical scientist during formulation development to investigate the relationship between tablet excipients and polymeric film-coating formulations (6).

MAJOR FORCES AFFECTING FILM–TABLET ADHESION

The two major forces that have been found to affect polymer–tablet adhesion are (*i*) the strength of the interfacial bonds and (*ii*) the internal stresses in the film. Hydrogen bond formation is the primary type of interfacial bonding between the tablet surface and polymer for pharmaceutical products (7). To a lesser extent, dipole–dipole and dipole-induced dipole interactions also occur. Factors that affect either the type or the number of bonds formed between the polymer and the solid surface will influence film adhesion.

When a polymeric solution or dispersion is applied to a substrate, internal stresses inevitably develop within the film (8). These stresses include stress due to shrinkage of the film as the solvent evaporates, thermal stress due to the difference in thermal expansion of the film and the substrate, and volumetric stress due to the change in volume when the substrate swells during storage. The total stress within a film is the sum of all the stresses acting on the polymer, and several researchers have developed equations to estimate total stress (8–11). Equation 1, developed by Okutgen et al. (12), includes contributions of volumetric changes of the tablet core in addition to the other well-established mechanisms:

$$P=\frac{E}{3(1-\nu)}\left[\frac{\Phi_s-\Phi_r}{1-\Phi_r}+\Delta\alpha_{(cubic)}\Delta T+\frac{\Delta V}{V}\right] \quad (1)$$

where P is the total internal stress in the film, E is the elastic modulus of the film, ν is the Poisson's ratio of the polymer, Φ_s represents the volume fraction of the solvent at the solidification point of the film, Φ_r is the volume fraction of solvent remaining in the dry film at ambient conditions, $\Delta\alpha_{(cubic)}$ is the difference between the cubical coefficient of thermal expansion of the film coat and the substrate, ΔT represents the difference between the glass transition temperature of the polymer and the temperature of the film during manufacturing and storage, ΔV is the volumetric change of the tablet core, and V denotes the original volume of the tablet core. Although this equation has been derived for polymeric solutions, the theory is applicable to polymeric dispersions as well. It is apparent from Equation 1 that the total stress within a film is directly proportional to the elasticity of the polymer. Factors that influence the elastic modulus of the polymer will, therefore, affect internal stress and film–tablet adhesion.

METHODS USED TO ASSESS POLYMER ADHESION

A distinction must be made between "fundamental" and "practical" adhesion. Fundamental or "true" adhesion refers to the intermolecular interactions between the polymer and the substrate (13). Practical or "measured" adhesion refers to the numerical value that results from a variety of testing methods, including shear and tensile tests. In addition to the interfacial interactions, other factors such as stresses in the film and the adhesion measurement technique will influence measured adhesion (11). No methods used to quantify polymer adhesion, however, can be directly used to measure fundamental adhesion.

The small size of the tablet and the nonuniform surface roughness of the substrate have presented significant challenges to the pharmaceutical scientist in determining the adhesive properties of a polymer (14,15). The earliest method for assessing adhesion of thin polymeric films to surfaces was the "Scotch tape" test (16), where a piece of adhesive tape was applied to the film surface and then peeled off. The film either adhered to the solid surface or was removed with the adhesive tape. This method was obviously qualitative in nature and did not provide an accurate measurement of polymer adhesion.

Another method that has been used to provide qualitative information regarding adhesion of polymers to pharmaceutical solids is diametral compression of coated substrates (17). During compression experiments, the total load will be distributed between the film coating and the solid substrate (5). The simultaneous fracture of the coating and the substrate is indicative of good adhesion between the polymer and the solid (17,18).

The first quantitative adhesion test was developed by Heavens in 1950 and was known as the "scratch test" (19). In this technique, the tip of a hard stylus is drawn across the surface of the film. The critical load required to completely detach the film from the substrate along the track of the scratch is determined and related to polymer adhesion. Although it is used extensively to study the adhesion of films cast onto metal surfaces, this method is unsuitable for pharmaceutical systems due to the relative rough surface of tablet compacts (20).

In the 1970s, the peel test was a popular method for the determination of film adhesion to tablets. The peel test uses a modified tensile tester to peel the film from the surface of the tablet at a 90° angle (21). The primary deficiency of this method is that the peel angle measured at the tablet surface is dependent on the elasticity of the film and the uniformity of adhesion, both of which can produce significant deviations in the data (15).

Several variations of the butt adhesion technique have been reported in the pharmaceutical literature over the past 20 years (22–26). This method is similar to the peel test. However, the entire film is removed normal to the surface of the tablet, rather than sections of the film being peeled. The butt adhesion technique eliminates variations due to the elasticity of the film and is less influenced by the uniformity of adhesion. The experimental set-up requires that the film coating around the edge of the tablet be removed using a scalpel. Next, the tablet is affixed to a lower, stationary platen. Double-sided adhesive tape is placed between the tablet surface and the upper platen. Rubber backing may be used to ensure adequate contact. A uniform displacement rate should be used to remove the film from the substrate (27). In 1980, Rowe (27) investigated the rate effects on measured adhesion of film coatings. Small increases in measured adhesion were found when the crosshead speed was increased from 0.1 to 1.5 mm/sec, whereas decreased adhesion resulted when the deformation rates were increased above 1.5 mm/sec, as shown in Figure 1.

The rates of deformation influence the rheological behavior of different components in the system, including the adhesive tape as well as the polymer itself, and, therefore, they affect how the applied stress is transmitted and distributed at the film–tablet interface (27). Higher rates of deformation resulted in an uneven stress distribution, thus lowering the measured adhesion.

Felton and McGinity (23) used a Chatillon digital force gauge and motorized test stand to conduct butt adhesion experiments. The apparatus was connected to a personal computer and force–deflection diagrams were constructed from the data, which permitted the visualization of the development of the force within the sample during the adhesion experiments. An example of a force–deflection diagram generated from this equipment is shown in Figure 2.

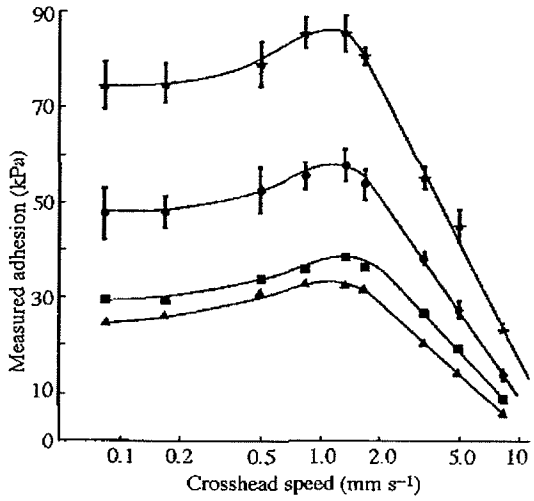

Figure 1 The effect of crosshead speed on measured adhesion of an organic-based cellulosic film. (★) Microcrystalline cellulose tablet core, 18 μm film thickness (Pharmacoat® 606); (●) microcrystalline cellulose tablet core, 70 μm film thickness (Pharmacoat 606); (■) lactose tablet core, 35 μm film thickness (Pharmacoat 606); (▲) lactose tablet core, 35 μm film thickness (Methocel® E 50). *Source*: From Ref. 27.

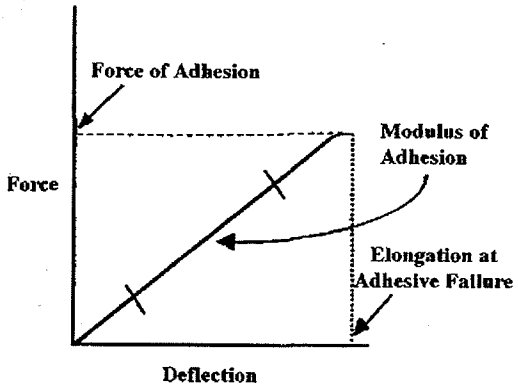

Figure 2 Example of a force–deflection profile generated using a Chatillon digital force gauge and motorized test stand to quantitate polymer adhesion by employing a butt adhesion technique. *Source*: From Ref. 23.

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The profile is similar to the stress–strain diagram commonly generated in the tensile testing of free films. From the force–deflection diagrams, the elongation at adhesive failure, the modulus of adhesion, and the adhesive toughness of the polymer, in addition to the force of adhesion, can be determined. The elongation at adhesive failure, analogous to the elongation at break obtained from tensile testing of free films, reflects the ductility of the polymer. The adhesive toughness is calculated as the area under the force–deflection diagram and is equal to the work required to remove the film from the surface of the solid.

An important factor to consider in the experimental design for investigating polymer adhesion is the shape of the tablet. In 1977, Rowe (28) compared the adhesive force between organic-based cellulosic films and either flat-faced or biconvex tablets. The force required to remove the film from the surface of the biconvex tablets was lower than the same films coated onto flat-faced tablets. A direct relationship between the force of adhesion and the square of the diameter of flat-faced tablets was found, whereas a maximum force was reached with biconvex table and no such correlation occurred. Interestingly, a direct relationship between the work required to remove the film from the tablet surface and the square of the diameter of the tablet was found for both flat-faced and biconvexed tablets. These findings suggest that the work done to remove the film from the tablet surface provides a more accurate and quantitative measure of film–tablet adhesion for biconvex tablets than the direct force measurement, whereas investigation of either the adhesive force or the adhesive toughness would be useful in the study of adhesion involving flat-faced tablets.

The majority of published studies investigating adhesion of polymeric films to pharmaceutical solids involve flat-faced tablets (15,22,23). Flat-faced tablets, however, may agglomerate in the coating pan apparatus during the coating process. Nonuniform adhesion of the polymer at the edge of the tablets has also been reported due to the high internal stresses within the film at the tablet edge (11,29). In a study conducted by Felton and McGinity (23), flat-faced punches with a beveled edge were used to achieve a more uniform adhesion of the polymeric film. The bevel decreased the sharp angle at the edge of the tablet and lowered the internal stresses within the film.

Film Thickness

Theoretically, film thickness should not affect the intrinsic adhesion at the film–tablet interface, with no influence on adhesion expected after the initial coverage of the substrate. Researchers, however, have found that polymeric film thickness will influence the measured force of adhesion. Rowe (14), for example, showed that for films up to a thickness of 35 μm, increased film thickness resulted in decreased adhesion of an organic-based cellulosic polymer, while films greater than 35 μm in thickness exhibited increased adhesion with increased film thickness. Similar results were reported for aqueous- and organic-based hydroxypropyl cellulose (HPC) (24) and aqueous-based acrylic polymeric films (23).

The effect of film thickness on measured adhesion is thought to be a property of the test method and associated with changes in the stress distribution within the film during the adhesion experiment (14). During the adhesion test, these stresses will either augment or oppose the applied stress and, therefore, influence measured adhesion. Extrapolation of the force of adhesion to a zero film thickness has been suggested by Reegen and Ilkka (30) as a method of minimizing the effects of residual stresses within a film. In most cases, however, a linear relationship between polymer adhesion and film thickness does not occur, and extrapolation of the force of adhesion to zero film thickness, therefore, would be difficult (14,24). Furthermore, measured film thickness is a mean value and does not account for variations in thickness that occur when the polymer is applied to the tablet (14).

SUBSTRATE VARIABLES

The physical and chemical characteristics of the substrate can significantly influence the adhesive properties of polymeric films. For example, the measured force of adhesion has been shown to be directly related to the square of the diameter of the tablet for flat-faced tablet compacts (15). In addition, the size of the substrate may also affect the error in the data, with higher coefficients of variation in the adhesive force occurring when testing small tablets, due to the difficulties involved in removing the film from the edge of the tablets (15). The following section describes some of the major substrate variables that impact polymer adhesion.

Surface Roughness

Surface roughness of a tablet and the force of compression used during the tableting process will affect polymer adhesion by altering the effective area of contact between the film coating and the surface of the solid. Above a critical compression force, increased compression pressure during tableting generally results in decreased adhesion, as a smoother tablet is produced. Below a critical compression pressure, cohesive failure of the tablet will occur, where the tablet laminates rather than the film being separated from the tablet surface. This type of failure occurs when the intermolecular bonding forces between the film and the tablet surface are stronger than the bonds between the powdered particles within the tablet (23). In contrast, adhesive failure of film-coated tablets will result in the coating being completely removed from the tablet surface with a minimal amount of powdered particles attached. In order to study film–tablet adhesion, the experimental parameters should be designed such that failure of the film is adhesive in nature (15,23). Data from cohesive failure should not be compared to data from adhesive failure, due to the different forces that are involved in these processes.

In a study involving an aqueous-based acrylic polymeric dispersion, Felton and McGinity (23) demonstrated a relationship between tablet hardness and polymer adhesion. Force–deflection profiles, as seen in Figure 3, show that as the tab-

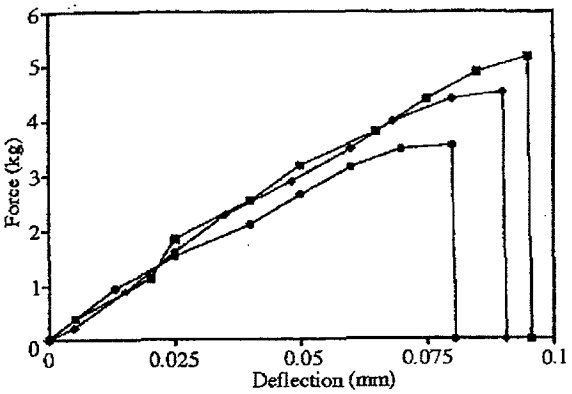

Figure 3 Force–deflection profiles obtained from butt adhesion experiments of an aqueous-based acrylic resin copolymer as a function of tablet hardness: (■) 7 kg; (♦) 10 kg; (●) 14 kg. *Source*: From Ref. 23.

let hardness was increased, the force of adhesion, elongation at adhesive failure, and the adhesive toughness of the acrylic polymer decreased.

The softer tablets possessed a relatively rougher surface, as evidenced by a higher arithmetic mean and root-mean-square roughness. The rougher surfaces of the tablet provided greater interfacial contact with the polymeric film, thus resulting in stronger polymer adhesion. Using a peel test, Nadkarni et al. (1) also found that the compressional force used during tableting influenced the adhesion of poly(methyl vinyl ether/maleic anhydride). Using contact angles between the polymeric solution and the tablet surface, these researchers showed that rougher tablets were more readily wetted by the polymeric solution.

In addition to surface roughness, tablet porosity can influence polymer adhesion. Polymeric films are generally applied to solid dosage forms using a spray atomization technique, and the water in the atomized droplets causes dissolution of the outermost surface of the tablet (26,31). The rate and depth of polymer solution/dispersion penetration will influence the interfacial contact between the polymer and the tablet, with the more porous tablet allowing faster penetration of the polymeric solution (15). Moreover, drugs and excipients from the tablet can physically mix with the coating (26,31) and affect the adhesive, mechanical, and drug-release properties of the polymer (23,32,33).

Tablet Excipients

Adhesion between a polymer and a substrate is due to the intermolecular bonding forces. For pharmaceutical products, hydrogen bond formation is the primary type of interfacial contact between the film and the tablet surface (7). Excipients used

in tablet formulations can alter the chemical properties of the tablet surface, thus influencing polymer adhesion. Sustained-release wax matrix tablets, for example, are generally difficult to coat with aqueous polymeric dispersions due to the poor wettability of the hydrophobic tablet surface (34).

The influence of direct-compression filler excipients on adhesion of organic-based hydroxypropyl methylcellulose (HPMC) films was investigated by Rowe (2). Polymer adhesion was found to be strongest when microcrystalline cellulose (MCC) was used in the tablet compacts. The interaction between the primary and secondary hydroxyl groups of HPMC and MCC was greater than with other excipients studied, including sucrose, lactose, and dextrose, due to the saturation of the tablet surface with hydroxyl groups (35). Lehtola et al. (22) found similar results with aqueous-based HPMC. HPMC phthalate was also found to adhere more strongly to MCC tablet compacts than tablets containing lactose or calcium phosphate (26).

Lubricating agents used in tablet formulations may influence polymer adhesion by presenting surfaces consisting of mainly nonpolar hydrocarbon groups, and the extent of the effect is dependent on the nature and concentration of the lubricant. Rowe (2) showed that increased concentrations of stearic acid, a commonly used lubricating agent that has a free polar carboxyl group, improved adhesion of an organic-based cellulosic polymeric film, as shown in Figure 4A.

When this group was combined with glycerol to form the glyceryl esters present in hydrogenated castor oil and vegetable stearin, polymer adhesion decreased, as seen in Figure 4B. Similar results were reported by Lehtola et al. for aqueous-based HPMC films (22). More recently, Felton and McGinity (23), investigating an aqueous-based acrylic polymer, found that adhesion decreased

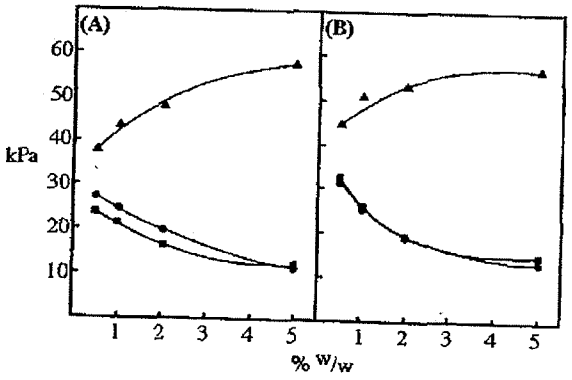

Figure 4 The effect of lubricant concentration (% w/w) on the measured adhesion (kPa) of hydroxypropyl methylcellulose films: (A) Pharmacoat® 606; (B) Methocel® 60HG viscosity 50; (▲) stearic acid; (●) magnesium stearate; (■) calcium stearate. Source: From Ref. 2.

when the concentration of the hydrophobic filler hydrogenated castor oil was increased in tablet compacts.

Adhesion to Capsules

Difficulties reported in the film coating of hard gelatin capsules have been attributed to the physical properties of the gelatin and the dosage form itself (36). In addition to the capsule shell softening and becoming sticky during the coating process due to solubilization of the gelatin, poor adhesion of the polymer to the walls of the hard gelatin capsule may occur. Insufficient adhesion may result in splintering of the film coating. The capsule shell is relatively smooth and generally provides less surface area for interfacial contact between the polymer and the surface of the gelatin than tablet compacts (37,38). The addition of polyethylene glycol (PEG) 400 and PEG 6000 to the coating formulation has been used to improve adhesion of polymeric films to the gelatin shell (36). An aqueous–alcoholic solution has also been shown to enhance polymer adhesion to capsule shells (38). Several studies suggest that hard-shell cellulosic capsules have a relatively rougher surface than the gelatin capsule and thus can provide better film adhesion (39,40).

Felton et al. (17) conducted diametral compression experiments on film-coated soft gelatin capsules and found that adhesion of an aqueous-based acrylic polymer was dependent on the fill liquid of the capsule in conjunction with the plasticizer used in the coating formulation. Good polymer adhesion resulted, as evidenced by single-point failure during compression of the coated capsules (5,18), when triethyl citrate (TEC) was incorporated into the coating formulation, regardless of the fill liquid. When the more hydrophobic plasticizer tributyl citrate (TBC) was added to the coating formulation, polymer adhesion was dependent on the fill liquid of the soft gelatin capsule, with better adhesion occurring with the hydrophobic Miglyol® 812 (Sasol GermanyGmbH, Witten, Germany) fill liquid compared to the hydrophilic PEG 400.

COATING VARIABLES

Since the strength of adhesion between the film and substrate surface is dependent on the number and type of interfacial interactions, different polymers will exhibit different adhesive properties, depending on their chemical structures. In addition to the polymer itself, film-coating formulations generally include a solvent, a plasticizing agent, an antiadherent, and pigments, all of which may also influence polymer adhesion. The following section describes some of the major coating formulation components that impact polymer adhesion.

Solvents

The solvent used in a film-coating formulation will interact with the polymer and affect the random coil structure of the polymer chains. It is generally accepted that

the greater the polymer–solvent interaction, the greater the end-to-end distance, thus exposing more of the polymer which is capable of interacting with and binding to the surface of the solid. Nadkarni et al. (1) suggested that the solubility parameter of the solvent be used as a qualitative measure of the extent of polymer solvation, with greater polymer solvation resulting in greater film–tablet adhesion. A good correlation between the cohesive energy density of the solvent and the peel strength of methyl methacrylate films coated on a tin substrate was found by Engel and Fitzwater (41). In 1988, Rowe (42) developed equations using solubility parameters of tablet excipients and polymers to predict trends in film–tablet adhesion.

Early research on film–tablet adhesion focused primarily on organic-based cellulosic films, and several studies have been published on the effects of solvent systems used in the coating formulation on polymer adhesion. Wood and Harder (21) used contact angle measurements, as an indication of surface wettability, to predict polymer adhesion. Fung and Parrott (6) compared the force of adhesion of HPC films prepared from several solvent systems and found that the force of adhesion varied twofold. Adhesion of films prepared from an aqueous-based system was one-fourth to one-half that of the organic-based films. These results further emphasize the importance of polymer–solvent interaction, since it is the polymer that must interact with and bind to the substrate.

Additives in the Coating Formulation

Plasticizers

Plasticizers are included in film-coating formulations to improve the mechanical and film-forming properties of the polymers (43–45). Several studies have focused on the effects of plasticizing agents on the adhesive properties of polymers. Felton and McGinity (46) investigated the influence of plasticizers on the adhesive properties of an acrylic resin copolymer to both hydrophilic and hydrophobic tablet compacts. Increasing the concentration of the hydrophilic plasticizer TEC in the coating formulation from 20% to 30% caused a slight, insignificant decrease in the force of adhesion. These results are in agreement with those of Fisher and Rowe (15), who found only slight, insignificant decreases in the measured force of adhesion between organic-based HPMC films and tablet compacts when the concentration of propylene glycol was increased from 10% to 20%. Felton and McGinity (46) showed that the plasticizer concentration also influences the elongation at adhesive failure. Moreover, these researchers demonstrated a relationship between the adhesive and mechanical properties of the acrylic polymer and suggested that the elongation at adhesive failure and the adhesive toughness of the polymer in conjunction with the force of adhesion provided a more complete understanding of the mechanisms involved in polymer adhesion.

Felton and McGinity (46) further investigated the effects of hydrophilic and hydrophobic plasticizers on polymer adhesion and found a relationship between adhesion and the glass transition temperature (T_g) of the film, with stronger adhesion occurring when the T_g of the film was lower, as shown in Table 1.

Table 1 Influence of the Plasticizer in the Coating Formulation on the Force of Adhesion and the Glass Transition Temperature (T_g) of an Acrylic Resin Copolymer to Lactose-Containing Tablets

Plasticizer	Force of adhesion (S.D.)	T_g (S.D.)
Triethyl citrate	4.85 kg (0.27)	36.5°C (1.1)
Polyethylene glycol 6000	4.32 kg (0.25)	38.6°C (2.5)
Tributyl citrate	3.81 kg (0.30)	51.2°C (2.2)
Dibutyl sebecate	3.48 kg (0.33)	62.0°C (3.6)

Source: From Ref. 3.

The water-soluble plasticizers, TEC and PEG 6000, lowered the T_g of the films to a greater degree than the hydrophobic plasticizers, TBC, and dibutyl sebecate, and films containing the hydrophilic plasticizers exhibited stronger adhesion. The researchers attributed these findings to the extent of the polymer–plasticizer interactions and the effectiveness of the plasticizing agent in lowering the internal stresses within the film coating. The addition of plasticizing agents to coating formulations generally decreases the internal stresses within the film by decreasing both the elastic modulus (E) and the glass transition temperature (T_g) of the film coating (11,47,48).

The influence of plasticizers in the coating on adhesion to hydrophilic and hydrophobic tablet compacts was also investigated (46). Adhesion of the films

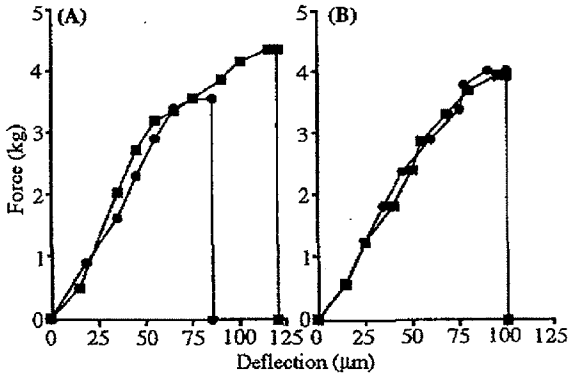

Figure 5 Force–deflection profiles obtained from butt adhesion experiments of an aqueous-based acrylic resin copolymer as a function of plasticizer type and tablet hydrophobicity: (A) 20% (w/w) polyethylene glycol 6000; (B) 20% (w/w) tributyl citrate; (■) 0% hydrogenated castor oil in tablet core; (●) 30% hydrogenated castor oil in tablet core. *Source*: From Ref. 46.

plasticized with PEG 6000 was found to be significantly influenced by the hydrophobicity of the tablet surface, as shown in Figure 5A.

These findings are in agreement with previous research showing that increasing tablet hydrophobicity decreased adhesion of both cellulosic and acrylic polymers (2,23). Interestingly, when TBC was incorporated into the coating formulation, no significant differences in the adhesive properties of the acrylic film were found, as seen in Figure 5B. Furthermore, these findings were correlated with thermomechanical data, where the T_g of the films plasticized with PEG 6000 was dependent on tablet hydrophobicity, while the amount of wax in the tablet core was not found to affect the T_g of the TBC-plasticized polymer.

Pigments and Fillers

Conflicting reports have been published on the influence of fillers or pigments on polymer adhesion to various substrates. Adhesion of ethylcellulose films cast on aluminum surfaces decreased with the addition of chalk, whereas the incorporation of talc into cellulosic films improved polymer adhesion (49). The addition of titanium dioxide and ferric oxide to methyl methacrylate films sprayed onto polymeric and tin substrates had no effect on adhesion, while mica and talc were found to decrease adhesion (41). Okhamafe and York (4) suggested that the effects of additives in coating formulations were dependent on the balance between their influence on the internal stress of the film coating and the strength of the film–tablet interface.

Several studies have investigated the influence of talc in coating formulations on the adhesion of polymers to tablet compacts. Talc is a hydrophobic substance that is generally added to the coating formulation to reduce the tackiness of the lacquer during the coating process. Talc has been found to decrease the adhesion of polymers to tablet compacts (4). The hydrophobic particles become embedded within the polymeric film and interfere with hydrogen bond formation between the tablet surface and the film coating. In addition, talc causes a stiffening of the film and increases the internal stresses within the polymer, as evidenced by an increase in the T_g of the polymer (50,51).

Pigments commonly used in pharmaceutical systems include aluminum lakes of water-soluble dyes, opacifiers such as titanium dioxide, and various inorganic materials including the iron oxides. Pigments differ significantly in their physical properties, including density, particle shape, particle size, and morphology, and these differences contribute to the complex relationship with aqueous film coatings (52–54). In addition to affecting the mechanical properties of films, the incorporation of pigments into coating formulations has also been found to influence polymer adhesion. Fisher and Rowe (15), for example, found a 45% reduction in the force of adhesion of HPMC films with the addition of 10% titanium dioxide to the coating formulation. Okhamafe and York (50) showed that increased concentrations of titanium dioxide produced an increase in the T_g of HPMC films, which the authors attributed to the restriction in the mobility of the polymer chains by the presence of the additives.

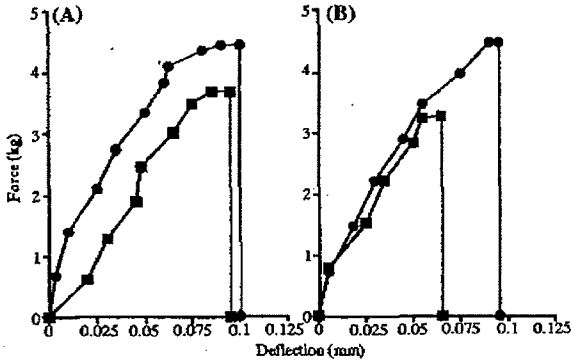

Figure 6 Force–deflection profiles obtained from butt adhesion experiments of aqueous-based Opadry® and Opadry® II as a function of tablet hydrophobicity: (A) 0% hydrogenated castor oil in tablet core; (B) 30% hydrogenated castor oil in tablet core; (■) Opadry; (●) Opadry II. *Source*: From Ref. 3.

Felton and McGinity (55) conducted a study that compared the adhesive properties of Opadry® and Opadry® II, two complete HPMC film-coating systems commercially available from Colorcon (West Point, Pennsylvania, PA). The Opadry II product was formulated with maltodextrins to achieve better adhesion, especially to hydrophobic substrates. Indeed, the addition of the maltodextrins to the cellulosic coating system enhanced polymer adhesion to both hydrophilic and hydrophobic tablet compacts, as shown in Figure 6.

Surfactants

Previous researchers have used the wettability of a tablet by a polymeric solution as a tool to predict the strength of film–tablet adhesion (1,56). A polymer solution that spreads more readily across the tablet surface allows for more interactions with the polymer chains and the formation of a greater number of bonds. Many of the polymeric materials commercially available today, however, are formulated as aqueous-based dispersions. Since it is the polymer, not the solvent, that interacts with and adheres to the tablet surface, wettability by polymeric dispersions may not be a valid indicator of film–tablet adhesion.

Surfactants have been incorporated into polymeric solutions to improve the spreadability of the coating across the tablet (57), emulsify water-insoluble plasticizers in aqueous dispersions (47,58), and modulate drug release (59,60). Felton et al. used surfactants to alter tablet wettability by polymeric dispersions (61). While the contact angle between the polymer dispersion and the tablet surface was dependent on the type and concentration of the surfactants added to the

coating formulation, no correlation between tablet wettability and polymer adhesion was found.

PROCESSING PARAMETERS AND COATING CONDITIONS

The magnitude of internal stresses that inevitably develop during the coating process is dependent upon the interrelationship between many parameters involving both the polymeric coating material and the core substrate (12). These stresses include stress due to shrinkage of the film upon solvent evaporation, thermal stress due to the difference in the coefficient of thermal expansion of the substrate and polymer, and volumetric stress due to the swelling or contraction of the substrate (8). Processing parameters may influence the development of these stresses. Okutgen et al. (62), for example, determined the dimensional changes in tablet cores as a function of temperature, simulating temperature variations that tablets generally undergo during the coating process. Tablets containing Avicel® (FMC Biopolymer, Philadelphia, Pennsylvania) maize starch, and Starch® 1500 (Colorcon, West Point, Pennsylvania) all contracted when exposed to elevated temperatures and expanded during the cooling phase, while Emcompress® (JRS Pharma, Patterson, New York) tablets exhibited the opposite behavior. These dimensional changes in the tablet core will influence the internal stresses within the films of the final coated products and may ultimately affect polymer adhesion. Selection of tableting excipients and polymeric coating materials with similar coefficients of thermal expansion should minimize internal stresses within the film and could improve polymer adhesion (11).

The process of film formation from polymeric dispersions requires the initial deposition of the atomized polymer droplets onto the substrate surface, followed by evaporation of the water, and subsequent coalescence of the polymer chains. The time necessary to form a completely coalesced film has been shown to be dependent on the temperature used during the coating process, the nature and concentration of the plasticizer incorporated into the coating formulation, and the postcoating storage temperature (63,64). Many commercially available polymeric materials for pharmaceutical film-coating operations require a postcoating thermal treatment or curing step to obtain a fully coalesced film, and this postcoating drying has also been shown to influence adhesion as well as the thermomechanical properties of the film (65). Storage at elevated temperatures was found to increase the force required to separate an acrylic film from the tablet surface, with adhesion equilibrated within four hours of storage at 40°C or 60°C (65). These findings were attributed to an increased number of polymer–substrate interactions resulting from the coalescence of the film. As the solvent evaporates during curing, the polymer droplets coalesce, and the number of potential polymer–substrate binding sites increases, as shown in Figure 7.

In addition to processing temperature and postcoating curing, the spray rate will influence the extent of surface dissolution of the substrate and subsequent interfacial mixing at the film–tablet interface (31). As mentioned previously, surface dissolution and physical mixing at the interface allows for drugs or excipients

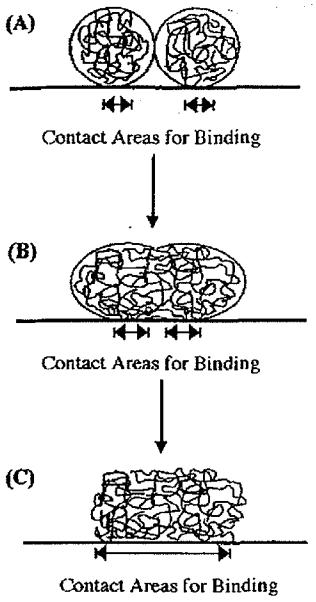

Figure 7 Schematic of the increase in potential polymer–substrate interactions as film formation proceeds: (A) closely packed polymer spheres due to water evaporation; (B) initiation of coalescence and polymer chain interdiffusion due to additional water evaporation; (C) completed film formation. *Source*: From Ref. 65.

in the tablet to migrate into the film (31), which can influence internal stresses and thus affect polymer adhesion.

Influence of Aging and Storage Conditions on Polymer Adhesion

Exposure of coated solids to various temperatures or relative humidities can influence the internal stresses within a film coating and thus affect polymer adhesion. Okhamafe and York (4), for example, showed that adhesion of pigmented and nonpigmented cellulosic films decreased during storage at 37°C and 75% relative humidity (RH). In another study, two weeks of storage at high RH (93%) caused a decrease in adhesion of an acrylic polymer to lactose tablets (46). These findings were attributed to increased internal stresses in the polymeric films due to differences in the expansion coefficient of the polymer and tablet, and volumetric stresses due to the swelling of the tablet core. Although previous researchers have demonstrated that water functions to plasticize polymers (66,67), the swelling of the film and the tablet as water diffuses through the coating during storage weakened the film–tablet interfacial bonding and created new stresses within the polymer.

Felton and McGinity (46) also reported decreased film–tablet adhesion after three months of storage at 0% RH. These findings were attributed to increased internal stresses within the coating due to evaporation of residual water in the polymeric film. Three months of storage at 40°C resulted in no significant change in the measured force of adhesion, with only small decreases in the elongation at adhesive failure and adhesive toughness. The authors suggested that, since the tablets were stored at a temperature above the T_g of the film, the polymer chains were more mobile (68) and positioned themselves to minimize internal stresses.

Decreased adhesion between a polymeric film and a capsule shell has been reported to occur during the storage of film-coated hard gelatin capsules at high humidity (36). The film coating and the gelatin swell to varying degrees and affect the internal stresses within the film. In another study involving film-coated soft gelatin capsules (17), storage at high humidity was found to improve adhesion of an acrylic polymer plasticized with TBC to the capsule containing PEG 400 as the fill liquid. The authors theorized that the fill liquid from the capsule may migrate into the film coating, functioning to further plasticize the polymer and lower the internal stresses of the film.

CONCLUSIONS

Although good adhesion between a polymer and the surface of a solid is desirable for a pharmaceutical product, limited research on polymer adhesion has been conducted on systems of pharmaceutical interest. The two major forces that influence adhesion are the strength of the interfacial bonds and the internal stresses within the film. Factors that influence interfacial bonding or internal stresses will therefore affect polymer adhesion. Rougher, more irregular surfaces provide greater interfacial contact between the film and the tablet surface and generally provide for better adhesion. Excipients used in the substrate can also influence the extent of interfacial bonding between the polymeric film and the solid. Additives in the coating formulation, including the solvent system, plasticizer, and pigments, influence internal stresses and thus alter polymer adhesion. Processing parameters used during coating may also affect adhesion. Although many variables have been found to influence polymer adhesion, and direct comparison of the numerical values from one study to another is not practical, further experimentation involving adhesion of polymeric films to solid substrates will provide the pharmaceutical scientist with a better understanding of the mechanisms involved in polymer adhesion.

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Curriculum Vitae

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PERSONAL

Born: January 27, 1968 New York, New York, USA
Married: to Valentina Nardi, M.D.

EDUCATION

Riverdale Country Day School
Graduate cum laude, 1986

Brown University
B.S. Biological Sciences (Biology), magna cum laude, 1990

Johns Hopkins University School of Medicine
M.D./Ph.D. Received in 1997
Thesis: Control of Translation by a Novel, Rapamycin-sensitive Signaling Pathway
Advisor: Dr. Solomon H. Snyder, Department of Neuroscience

PRIMARY FACULTY/FELLOW APPOINTMENTS

Whitehead Institute for Biomedical Research, Cambridge, MA
Whitehead Fellow, Oct. 1997-Sept. 2002
Member, 2002-present
Massachusetts Institute of Technology, Department of Biology, Cambridge, MA
Assistant Professor, 2002-2005
Associate Professor, 2006-2007
Associate Professor with Tenure, 2008-present
Howard Hughes Medical Institute
Investigator, 2008-present

OTHER APPOINTMENTS

Broad Institute of Harvard and MIT, Cambridge, MA
Senior Associate Member, 2004-present

Koch Center for Integrative Cancer Research at MIT, Cambridge, MA

Member 2004-present

AWARDS AND FELLOWSHIPS

2005, David H. Koch Cancer Research Fellowship
2005, W. M. Keck Foundation Distinguished Young Scholars in Medical Research Fellowship
2005, Howard S. Stern and Linda B. Stern Career Development Professorship
2004, Rita Allen Fellowship
2003, Charles Ross Scholar Award, Massachusetts Institute of Technology
2003, Pew Scholar in the Biomedical Sciences
2003, Edith C. Blum Foundation Award
2002, Technology Review TR100 Young Innovator's Award, awarded by *Tech Review* magazine
1999, Skeggs Fellow, Whitehead Institute
1997, Michael A. Shanoff Award for Thesis Research, Johns Hopkins University School of Medicine
1990-1997, Medical Scientist Training Program Award
1994, Franklin P. Mall anatomy prize, Department of Cell Biology and Anatomy, Johns Hopkins University School of Medicine
1990, Honors, Biology Department, Brown University
1990, Sigma Chi Society

FUNDED GRANTS

"Regulation of the mTOR Growth Pathway by Nutrients"
National Institutes of Health Grant 1 RO1 CA103866
P.I. David M. Sabatini
Dates: March 2004 – June 2014
The goal of this award is to identify the molecular mechanisms through which the mTORC1 pathway senses nutrients by controlling the interaction between mTOR and raptor.

"Cell Growth Signaling in Cancer Development"
National Institutes of Health Grant 1RO1 CA129105
P.I. David M. Sabatini
Dates: April 2008 – January 2013
The goal of this award is to study growth control in cancer.

"Rapamycin-Insensitive Signaling by Rictor-mTOR"
National Institutes of Health Grant 1 R01 AI047389
P.I. David M. Sabatini
Dates: April 2005 - March 2010
The goals of this grant are to identify the components of the mTORC2 pathway and to understand its role in the tumorigenesis driven by the loss of the PTEN tumor suppressor.

"Metabolism and Phosphatase Regulation of the TOR Pathway"
National Institutes of Health Grant 1 RO1 GM072555
P.I. David M. Sabatini
Dates: April 2005 – December 2009
The major goals of this project are to understand how nutrients regulate the mTORC1 pathway and to identify a hypothesized phosphatase that negatively regulates mTOR.

"Structural and Mechanistic Analyses of the TSC1/2 and Rheb-Mediated Regulation of the mTOR Pathway"
DOD TSC Research Program Grant

P.I. David M. Sabatini
Dates: July 2007 - June 2010
The goals of this grant are to determine the structure by cryo-electron microscopy of mTORC1 and to understand the role of raptor phosphorylation in the regulation of the pathway.

"Regulatory Networks in Cancer Initiation & Progression" (RNAi Interference Core)
NIH (Subcontract)
PI: Lauffenburger
Dates: September 2006 - August 2009
The goal of this subcontract is to provide automated image analysis software using Cellprofiler software which was designed and implemented in the Sabatini Laboratory.

"Mammalian Target of Rapamycin (mTOR) Signaling in Health and Longevity"
Julie Martin Mid-Career American Federation for Aging
Dates: July 2009 – June 2013
The goal of this project is to better understand the effects of decreased mTOR signaling on mammalian health and aging.

"Identification of the Metabolic Adaptations that Allow Tumor Cells to Survive in Poorly-Vascularized Environments and Understanding their Roles in Tumorigenesis"
W.M. Keck Foundation
P.I. David M. Sabatini
Dates: July 2005 – June 2010
The major goal of this project is to identify the metabolic adaptations tumor cells use to survive in the poor-vascularized tumor environment and to understand the role of these adaptations in tumorigenesis.

"Development of a Chemostatic Cell Culture System to Study Cancer Cell Metabolism"
Stewart Trust Foundation
P.I. David M. Sabatini
Dates: July 2009 – June 2010
The goal of this project is to use a chemostatic system that to study the continuous culture of cancer cells under hypoxia as well as low but constant levels of important nutrients.

"Identification of the Molecular Drivers of Brain Tumor Stem Cell Functions"
National Brain Tumor Foundation
P.I. David M. Sabatini
Dates: May 2007 - April 2008
This is a pilot grant to set up an RNAi screen for 'stemness' genes in brain cancer stem cells.

"Role of Metabolic Signaling Pathways in Early Breast Tumor Development"
Stewart Trust Foundation
P.I. David M. Sabatini
Dates: July 2007 - June 2008
This is a pilot grant to set up a model system using tumor xenografts to study the mechanisms through which caloric restriction reduces tumorigenesis.

"Role of Metabolic Signaling Pathways in Early Breast Tumor Formation and Sensitivity to Calorie Restriction"
David H. Koch Cancer Research Fund
P.I. David M. Sabatini

Dates: July 2007 - May 2008
The goals of this grant are to characterize the differential sensitivities of different cancer cell lines to extracellular growth factors and nutrients in vitro. The influence of calorie restriction will then be assessed on the growth of different tumors in orthotopic/subcutaneous mouse models. From here we will be able to identify the signaling pathways that confer sensitivity of tumor cells to systemic energy status.

"High Throughput Experiments to Discover Novel Drug Target for the Treatment of Tuberous Sclerosis Complex"
DOD TSC Research Program Grant W81XWH-05-1-0318-DS
P.I. David M. Sabatini
Dates: January 2004 - June 2007
The goal of this research is to conduct genome-wide RNA interference experiments in Drosophila to identify genes which cause only cells deficient in TSC1 or TSC2 function to arrest, die, or revert to normal without disrupting normal remaining cells.

"Nutrient Signaling to the mTOR Growth Pathway"
Pew Scholars Program in the Biomedical Science
P.I. David M. Sabatini
Dates: July 2003 - June 2007
The goal of this award is to identify the genes, using cell-based microarrays, that generate the mitochondrially-derived signal that regulates the mTOR pathway.

"Identification of the Mitochondrially-derived Signal That Regulates Growth Through the mTOR Pathway"
Rita Allen Scholar Award
P.I. David M. Sabatini
Dates: September 2004 - August 2007
The goal of this award is to biochemically purify and test metabolites that may be sensed by the mTOR pathway.

"Building a Platform to Identify the Metabolic Adaptations that Allow Tumor Cells to Survive in Poorly-Vascularized Environments"
David H. Koch Cancer Research Fund
P.I. David M. Sabatini
Dates: February 2005 - January 2006
The major goal of this project is to fully implement a mammalian lentivirial RNAi screening platform for screening the effects of loss of metabolic gene expression on cancer cells.

"Identification of the Metabolic Pathways that Allow Cancer Cells to Survive in the Tumor Environment"
Alexander and Margaret Stewart Trust Cancer Pilot Research Award
P.I. David M. Sabatini
Dates: July 2005 - June 2006
The goal of this pilot grant is to set up an RNAi screening platform.

"Development of a Systematic Method for Studying the Activity of Individual Human Genes in Cancer Cells"
Blum Foundation
P.I. David M. Sabatini
Dates: July 2002 - December 2005

The goal of this project is to continue the development of a microarray-based method for the screening of drugs in cellular assays. Pilot experiments indicate that the method is functional and will enable at least a 100-fold increase in throughput over the currently available methods. This grant was shared with Brent Stockwell.

"Development of siRNA-Expressing Cell Microarrays for Identifying Genes That Participate In Alzheimers Disease".
The Fidelity Foundation
P.I. David M. Sabatini
Dates: September 2002 - August 2005
The goal of this grant is to make a collection of several thousand plasmid-based shRNAs that can then be used to create cellular microarrays in which the cells of each feature has a knock-down of a specific gene.

Patents

Patent 6544790: Reverse Transfection Method, issued 4/8/2003
Patent 6476200: Proteins that bind to FKBP12 in a rapamycin-dependent fashion, issued 11/5/2002
Drug Microarrays. Filed 7/10/2001
Nucleic Acids Encoding a Mammalian Raptor Polypeptide and Uses Thereof, filed 5/16/2002
GβL, a protein that binds the mTOR kinase domain and mediates raptor function, filed 2/18/2003
Transfection Method and Uses Related Thereto, filed 3/28/03

Books (or excerpts, or chapters)

Guertin, D. A., Kim, D.-H., and Sabatini, D. M., "Growth Control Through the mTOR Network" in *Cell Growth: Control of Cell Size* (Edited by Michael N. Hall, Martin Raff, and George Thomas), p.193-234. Cold Spring Harbor Laboratory Press, 2004.

Guertin, D.A and Sabatini, D.M., "Cell Size Control" in: *Encyclopedia of Life Sciences*. John Wiley & Sons, Ltd: Chichester, 2006.

Papers in Refereed Journals

1. Baccarini, M., Sabatini, D.M., App, H., Rapp, U.R. and Stanley, E.R., "Colony Stimulating factor-1 (CSF-1) stimulates temperature dependent phosphorylation and activation of the RAF-1 proto-oncogene product," EMBO *9*, 3649-3657, November 1990.

2. Sabatini, D.M., Erdjument-Bromage, H., Lui, M., Tempst, P. and Snyder S.H., "RAFT1: A Mammalian Protein That Binds to FKBP12 in a Rapamycin-Dependent Fashion and is Homologous to Yeast TORs," Cell *78*, 35-43, July 1994.

3. Erdjument-Bromage, H., Lui, M., Sabatini D.M., Snyder S.H. and Tempst, P., "High-sensitivity sequencing of large proteins: partial structure of the rapamycin-FKBP12 target," Protein Science *3*, 2435-2446, December 1994.

4. Cameron, A.M., Steiner, J.P., Sabatini, D.M., Kaplin, A.I., Walensky, L.D. and Snyder, S.H., "Immunophilin FK506 binding protein associated with inositol 1,4,5-triphosphate receptor modulates calcium influx," Proceedings of the National Academy of Sciences *92*, 1784-1788, February 1995.

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9. Burnett, P.E., Barrow, R.K., Cohen, N.A., Snyder, S.H. and Sabatini, D.M., "RAFT1 phosphorylation of translational regulators p70 S6 kinase and 4E-BP1," Proceedings of the National Academy of Sciences *95*, 1432-1437, February 1998.

10. Snyder, S.H., Sabatini, D.M., Lai, M.M., Steiner, J.P., Hamilton, G.S. and Suzdak, P.D., "Neural actions of immunophilin ligands," Trends in Pharmacological Sciences *19*, 21-26, January 1998.

11. Burnett, P.E., Blackshaw, S., Mai, M.L., Qureshi, I.A., Burnett, A.F., Sabatini, D.M. and Snyder, S.H., "Neurabin is a synaptic protein linking p70 S6 kinase and the neuronal cytoskeleton," Proceedings of the National Academy of Sciences *95*, 8351-8356, July 1998.

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20. Bailey, S., Wu, R. and Sabatini, D.M., "Applications of transfected cell microarrays to drug discovery," Drug Discovery Today, *High-throughput Technologies Supplement*, S113-118, September 2002.

21. Kim, D.-H., Sarbassov, D., Ali, S.M., King, J.E., Latek, R.R., Erdjument-Bromage, H., Tempst, P., and Sabatini, D.M., "mTOR interacts with raptor to form a nutrient-sensitive complex that signals to the growth machinery," Cell *110*, 163-175, July 2002.

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26. Kim, D.-H., and Sabatini, D.M., "Raptor and mTOR: subunits of a nutrient-sensitive complex," Current Topics in Microbiology and Immunology *279,* 259-270, 2004.

27. Carpenter, A.E. and Sabatini, D.M., "Systematic genome-wide screens of gene function," Nature Reviews Genetics *5,* 11-22, January 2004.

28. Sarbassov, D., Ali, S.M., Kim, D.-H., Guertin, D.A., Latek, R.R., Erdjument-Bromage, H., Tempst, P., and Sabatini, D.M., "Rictor, a novel binding partner of mTOR, defines a rapamycin-insensitive and raptor-independent pathway that regulates the cytoskeleton," Current Biology *14,* 1296-1302, July 2004.

29. Wheeler, D.B., Bailey, S.N., Guertin, D.A., Carpenter, A.E., Higgins, C.O, and Sabatini, D.M., "RNAi living cell microarrays for loss of function screens in Drosophila cells," Nature Methods *1*, 127-132, November 2004.

30. Bailey, S.N., Sabatini, D.M., and Stockwell, B.R., "Microarrays of small molecules embedded in biodegradable polymers for use in mammalian cell-based screens," Proceedings of the National Academy of Sciences *101,* 16144-16149, November 2004.

31. Sarbassov, D.D., Guertin, D.A., Ali, S.M., and Sabatini, D.M., "Phosphorylation and Regulation of Akt/PKB by the Rictor-mTOR complex," Science *307,* 1098-1101, February 2005.

32. Ali, S.M. and Sabatini, D.M., "Structure of S6K1 determines if raptor-mTOR or rictor-mTOR phosphorylates its hydrophobic motif site," Journal of Biological Chemistry *280*, 19445-19448, May 2005.

33. Wheeler, D.B., Carpenter, A.E., Higgins, and Sabatini, D.M., "Chipping away at gene function with RNAi cell microarrays," Nature Genetics *Supplement*, S25-30, June 2005.

34. Guertin, D.A. and Sabatini, D.M., "An expanding role for mTOR in cancer," Trends in Molecular Medicine *8*, 353-361, August 2005.

35. Sarbassov, D.D., Sabatini, D.M., "Redox Regulation of the nutrient-sensitive raptor-m-TOR pathway and complex," Journal of Biological Chemistry *280*, 39505-9. 2005.

36. Sarbassov, D.D., Ali, S.M., Sabatini, D.M., "Growing roles for the mTOR pathway," Current Opinion in Cell Biology *17*, 596-603. 2005.

37. Bailey, S.N., Ali, S.M., Sabatini, D.M., "Microarrays of lentiviruses for gene function screens in immortalized and primary cells," Nature Methods *3,* 117-22, March 2006.

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39. Moffat, J. and Sabatini, D.M., "Building mammalian signalling pathways with RNAi screens," Nature Reviews Molecular Biology *3*, 177-187, March 2006.

40. Sarbassov, D.D., Ali, S.A., Sengupta, S., Sheen, J.H., Hsu, P., Bagley, A.F., Markhard, A.L., and Sabatini, D.M., "Prolonged rapamycin treatment inhibits mTORC2 assembly and Akt/PKB," Molecular Cell *22*, 159-168, March 2006.

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42. Sabatini, D.M. "mTOR and cancer: insights into a complex relationship," Nature Reviews Cancer *9*, 729-734. September 2006

43. Frias, M.A. Thoreen, C.C., Jaffe, J.D., Schroder,W., Sculley, T., Carr, S.A. and Sabatini, D. M., "mSin1 Is Necessary for Akt/PKB Phosphorylation, and Its Isoforms Define Three Distinct mTORC2s," Current Biology *16*, 1-6, September 2006.

44. Root, D.E., Hacohen, N., Hahn, W.C., Lander, E.S., Sabatini, D.M., "Genome-scale loss-of-function screening with a lentiviral RNAi library," Nature Methods *3*, 715-19, September 2006.

45. Reiling, J.H. and Sabatini, D.M., "Stress and mTORture Signaling," Oncogene *25*, 6373–6383. October 2006.

46. Carpenter, A. E., Jones, T. R., Lamprecht, M. R.., Clarke, C., Kang, I.H., Friman, O., Guertin, D.A. Chang, J.H., Lindquist, R. A., Moffat, J., Golland, J. and Sabatini, D. M., "CellProfiler: image analysis software for identifying and quantifying cell phenotypes". Genome Biology *7*:R100. October 2006.

47. Echeverri, C. J., Beachy, P. A., Baum, B., Boutros, M., Buchholz, F., Chanda, S. K., Downward, J., Ellenberg, J., Fraser, A. G., Hacohen, N., Hahn, W. C., Jackson, A. L., Kiger, A., Linsley, P. S., Lum,

L., Ma, Y., Mathey-Prévôt, B., Root, D. E., Sabatini, D.M., Taipale, J., Perrimon, N., and Bernards, R.. "Minimizing the risk of reporting false positives in large-scale RNAi screens," Nature Methods. *3*, 777-779. October 2006.

48. Guertin, D.A., Stevens D.M, Thoreen, C.C., Burds, A.A., Kalaany, N.Y., Moffat, J., Brown, M. Fitzgerald, K.J. and Sabatini, D.M., "Ablation in mice of the mTORC components raptor, rictor, or mLST8 reveals that mTORC2 is required for signaling to Akt-FOXO and PKCalpha, but not S6K1," Developmental Cell *11*, 859-871. December 2006.

49. Lamprecht, M.D., Sabatini, D.M., and Carpenter, A.E. "CellProfiler: free, versatile software for automated biological image analysis," Biotechniques *42*, 71-75. January 2007.

51. Zeng, Z., Sarbassov, D. D., Samudio, I. J., Yee, K., Munsell, M.F., Jackson, M.F., Ellen, J.C., Giles F. J., Sabatini, D.M., Andreeff, M. and Konopleva1, M.. "Rapamycin derivatives reduce mTORC2 signaling and inhibit AKT activation in AML," Blood *8*, 3509-12 April 2007.

52. Sancak, Y., Thoreen C.C., Peterson T.R., Lindquist R.A., Kang, S.A., Spooner E., Carr S.A., Sabatini, D.M., "PRAS40 is an insulin-regulated inhibitor of the mTORC1 protein kinase," Molecular Cell *6,* 903-15. March 2007.

53. Moffat J. Reiling J.H., and Sabatini D.M. "Off-target effects associated with long dsRNAs in Drosophila RNAi screens," Trends in Pharmacological Sciences *4*, 149-51. April 2007.

54. Guertin, D.A., and Sabatini, D.M., "Defining the Role of mTOR in Cancer," Cancer Cell *12*, 9-22, July 2007.

55. Reiling, J.H., and Sabatini, D.M., "Increased mTORC1 signaling UPRegulates stress," Molecular Cell *14,*533-535. March 2008.

56. Sancak, S., Peterson, T.R., Shaul, Y.D., Lindquist, R.A., Thoreen, C. C., Bar-Peled, L. and Sabatini, D.M., "The Rag GTPases bind raptor and mediate amino acid signaling to mTORC1," Science *320*, 1496-1501. May 2008.

57. Hsu, P.P. and Sabatini, D.M., "Cancer Cell Metabolism: Warburg and Beyond," Cell *134*, 703-707. September 2008.

58. Jones, T.R., Kang, I.H., Wheeler, D.B., Lindquist, R.A., Papallo, A., Sabatini, D.M., Golland, P., and Carpenter, A.E., "CellProfiler Analyst: data exploration and analysis software for complex image-based screens," BMC Bioinformatics *9*, 482. November 2008.

59. Luo, B., Cheung, H.W., Subramanian, A., Sharifnia, T., Okamoto, M., Yang, X., Hinkle, G., Boehm, J.S., Beroukhim, R., Weir, B.A., Mermel, C., Barbie, D.A., Awad, T., Zhou, X., Nguyen, T., Piqani, B., Li, C., Golub, T.R., Meyerson, M., Hacohen, N., Hahn, W.C., Lander, E.S., Sabatini, D.M., and Root, D.E., "Highly parallel identification of essential genes in cancer cells," PNAS *105*, 20380-203805. December 2008.

60. Thoreen, C.C., Kang, S.A., Chang, J.W., Liu, Q, Zhang, J., Gao, Y., Reichling, L.J., Sim, T., Sabatini, D.M., and Gray, N.S., "An ATP-competitive mTOR inhibitor reveals rapamycin-insensitive functions of mTORC1," J. Biological Chemistry, *284*, 8023-8032. January 2009.

61. Guertin, D.A., Stevens, D.M., Saitoh, M., Kinkel, S., Crosby, K., Sheen, J.-H., Mullholland, D.J., Magnuson, M.A., Wu, H., and Sabatini, D.M., "The mTOR complex 2 is required for the development of prostate cancer induced by PTEN loss in mice," Cancer Cell *15*, 148-159. February 2009.

62. Kalaany, N.K. and Sabatini, D.M., "Tumours with PI3K activation are resistant to dietary restriction," Nature *458*, 725-731. April 2009.

63. Peterson, T.R., Laplante, M., Thoreen, C., Sancak, Y., Kang, S. A., Kuehl, W. M., Gray, N. S., Sabatini, D. M., "DEPTOR is an mTOR Inhibitor Whose Frequent Overexpression in Multiple Myeloma Cells Promotes their Survival. Cell *137,* 873-886, May 2009.

Proceedings of Refereed Conferences

None

Other Major Publications

1. Thoreen, C.C. and Sabatini, D.M., "Huntingtin aggregates ask to be eaten," Nature Genetics *36,* 553-554, June 2004.

2. Peterson, T.R. and Sabatini, D.M., "eIF3: a connector of S6K1 to the translational preinitiation complex," Molecular Cell *20*, 655-657. December 2005.

3. Thoreen, C.C. and Sabatini, D.M., "AMPK and p53 help cells through lean times," Cell Metabolism *18*, 283-293. April 2005.

Internal Memoranda and Progress Reports

None

Invited Lectures

July 2001, "New Approaches to the Study of Cell Growth," *Cancer: Mechanisms and Models* Gordon Research Conference, Newport, Rhode Island.

August 2001, "Cell-Based Microarrays," Enabling Technologies for Alzheimer's Disease Workshop, Bar Harbor, Maine.

October 2001, "New Approaches to the Study of Cell Growth," Department of Pathology Seminars, Yale University.

December 2001, "Cell-Based Microarrays," Yokohama 21st Century Forum, Yokohama, Japan.

December 2001, "Cell-Based Microarrays," RIKEN Research Seminar, RIKEN at Yokohama, Japan.

January 2002, "Cell-Based Microarrays," Cambridge Healthtech *Protein Microarrays* Meeting, San Diego, California.

January 2002, "New Approaches to the Study of Cell Growth," Pharmacology Departmental Seminar, University of California at Los Angeles.

March 2002, "Cell-Based Microarrays," IBC *Protein/Cell Microarrays* Meeting, San Diego, California.

April 2002, "Cell-Based Microarrays," Proteomics Workshop, National Institutes of Health.

April 2002, "Cell-Based Microarrays," Cambridge Healthtech: *Macroresults through Microarrays* Meeting, Boston, Massachusetts.

August 2002, "Cell-Based Microarray Loss of Function Studies," Enabling Technologies for Alzheimer's Disease Workshop II, Bar Harbor, Maine.

August 2002, "The Role of the mTOR Pathway in Cancer," Targeted Therapies Meeting, Washington, D.C.

September 2002, "RNAi and Cell-Based Microarrays," Wyeth/GI RNAi Symposium, Cambridge, Massachusetts.

October 2002, "RNAi and Cell-Based Microarrays," Brazilian Congress of Pharmacology Meeting, Aguas de Lindoia, Brazil.

November 2002, "RNAi and Cell-Based Microarrays,"ACS Prospectives Meeting, Boston, Massachusetts.

November 2002, "New Approaches to the Study of Cell Growth," NYSEM Presidential Symposium, Cornell Medical College.

December 2002, "New Approaches to the Study of Cell Growth," 2nd International Conference on Structural Biology, Singapore.

January 2003, "New Approaches to the Study of Cell Growth," CSBi Symposium at MIT: *From Bioinformatics to Biofabrication*, Cambridge, Massachusetts.

January 2003, "The Control of Cell Growth by the mTOR Pathway," Molecular Genetics and Microbiology Departmental Seminar, Robert Wood Johnson Medical School.

February 2003, "The Control of Cell Growth by the mTOR Pathway," Cardiovascular Research Center Seminar, Massachusetts General Hospital.

February 2003, "New Approaches to the Study of Growth," ABRF 2003: *Translating Biology Using Proteomics and Functional Genomics* Meeting, Denver, Colorado.

February 2003, "New Approaches to the Study of Growth," Keystone Symposium: *Functional Genomics: Global Analysis of Complex Biological System*, Santa Fe, New Mexico.

April 2003, "The Control of Cell Growth by the mTOR Pathway," ASBMB: *mTOR symposium*, San Diego, California.

May 2003, "The Control of Cell Growth by the mTOR Pathway," Friday Noon Seminar, St. Jude Children's Research Hospital.

August 2003, "High-Throughput Loss of Function Studies Screening," Enabling Technologies for Alzheimer's Disease Workshop III, Bar Harbor, Maine.

August 2003, "The Control of Cell Growth by the mTOR Pathway," Research Seminar, Friedrich Miescher Institute, Basel, Switzerland.

August 2003, "The Control of Cell Growth by the mTOR Pathway," Arolla Workshop: *Cell Growth in Development and Disease,* Arolla, Switzerland.

August 2003, "The Role of the mTOR Pathway in Cancer," Targeted Therapies II Meeting, Washington, D.C.

October 2003, "The Control of Growth by the mTOR Pathway," *Translating Genomes: Proteomics and Beyond*, CABM, UMDNJ, Piscataway, New Jersey.

October 2003, "The Control of Growth by the mTOR Pathway," Division of Biology and Medicine Seminar, Brown University.

October 2003, "The Control of Growth by the mTOR Pathway," Science and Medicine Seminar, Department of Medicine, Massachusetts General Hospital.

November 2003, "The Control of Growth by the mTOR Pathway," Department of Genetics Seminar Series, Washington University.

December 2003, "The Control of Growth by the mTOR Pathway," Gastrointestinal Unit Research Seminar Series, Massachusetts General Hospital.

December 2003, "The Control of Growth by the mTOR Pathway," Molecular Medicine Seminar, Brigham & Women's Hospital.

December 2003, "Signaling by the mTOR Pathway," Research Seminar, Wyeth Research, Pearl River, New York.

January 2004, "Signaling by the mTOR Pathway," Research Seminar, Infinity Pharmaceuticals, Cambridge, Massachusetts.

February 2004, "Signaling by the mTOR Pathway," Research Seminar, Pfizer Discovery Technology Center, Cambridge, Massachusetts.

February 2004, "The Control of Growth by the mTOR Pathway," Seminars in Biomedical Science, University of California at San Francisco.

February 2004, "The Control of Growth by the mTOR Pathway," Institute for Cancer Genetics Seminar, Columbia University.

April 2004, "New Approaches to the Study of Growth Control," Lewis-Sigler Institute for Integrative Genomics Seminar, Princeton University.

April 2004, "The Control of Growth by the mTOR Pathway," Cellular and Molecular Physiology Departmental Seminar, Tufts University.

April 2004, "The Control of Growth by the mTOR Pathway," CMB/LSC Seminar Series, Penn State College of Medicine.

April 2004, "The Control of Growth by the mTOR Pathway," Abramson Cancer Institute Seminar, University of Pennsylvania.

April 2004, "New Approaches to the Study of Cell Growth," Research Seminar, Functional Genomics Workshop, Dana-Farber Cancer Institute.

April 2004, "New Approaches to the Study of Cell Growth," 3rd Annual International Symposium on Systems Biology, Institute for Systems Biology, Seattle, Washington.

April 2004, "The Control of Growth by the mTOR Pathway," Frontiers in Biology Seminar, Stanford University.

May 2004, "The Control of Growth by the mTOR Pathway," Department of Biochemistry Seminar, McGill University.

May 2004, "The Control of Growth by the mTOR Pathway," Workshop on Proteins Controlling Cell Growth, Institute Juan March, Madrid, Spain.

May 2004, "mTOR Signaling," Research Seminar, Novartis Institute for Biomedical Research, Cambridge, Massachusetts.

June 2004, "New Approaches to the Study of Cell Growth," Genomics, Proteomics & Bioinformatics session, ASBMB, Boston, Massachusetts.

June 2004, "The Control of Growth by the mTOR Pathway," Research Seminar, Ontario Cancer Institute, Toronto, Canada.

June 2004, "The Control of Growth by the mTOR Pathway," Research Seminar, Genetics Society of Canada, Toronto, Canada.

June 2004, "The Control of Growth by the mTOR Pathway," *2nd Messengers & Protein Synthesis* Gordon Research Conference, Meriden, New Hampshire.

June 2004, "mTOR Signaling," Boehringer Ingelheim Strategic Planning Meeting on Targets in Oncology, Vienna, Austria.

October 2004, "The Control of Growth by the mTOR Pathway," University Lecture, Rockefeller University.

October 2004, "The Control of Growth by the mTOR Pathway," Department of Pharmacology Research Seminar, New York University.

October 2004, "The Control of Growth by the mTOR Pathway," Division of Cancer Biology Research Seminar, Beth Israel Deaconess.

October 2004, "New Approaches to the Study of Cell Growth," Special Session, American Society of Human Genetics Annual Meeting, Toronto, Canada.

November 2004, "The Control of Growth by the mTOR Pathway," Oncology Seminar, Dana-Farber Cancer Institute.

November 2004, "The Control of Growth by the mTOR Pathway," Fall Cancer Symposium, University of Michigan Medical Center, Ann Arbor, Michigan.

January 2005, "Signaling by the mTOR Pathway," Research Seminar," OSI Pharmaceuticals, Farmingdale, New York.

January 2005, "The Control of Growth by the mTOR Pathway," Research Seminar, MGH/Harvard Cutaneous Biology Research Center, Massachusetts General Hospital.

January 2005, "New Approaches to the Study of Cell Growth," Research Seminar, Bauer Center for Genomics, Harvard University.

February 2005, "The Control of Growth by the mTOR Pathway," Research Seminar, MGH Center for Cancer Research, Massachusetts General Hospital.

March 2005, "The Control of Growth by the mTOR Pathway," Neuroscience Monday Seminars, Children's Hospital, Boston, Massachusetts.

March 2005, "RNAi Library Screening," TargetTalk Meeting, San Diego, California.

April 2005, "The Control of Growth by the mTOR Pathway," Department of Pharmacology Seminar Series, University of Virginia, Charlottesville, Virginia.

June 2005, "Regulation of Growth by the mTOR Pathway," Research Seminar, Pfizer Research Technology Center, Cambridge, Massachusetts.

June 2005, "Regulation of Growth by the mTOR Pathway," American Diabetes Association, San Diego, California.

July 2005, "Signaling by the mTOR Pathway," Research Seminar, GlaxoSmithKline, Philadelphia, Pennsylvania.

July 2005, "Regulation of Growth by the mTOR Pathway," *Cancer Models & Mechanisms* Gordon Research Conference, Smithfield, Rhode Island.

July 2005, "Control of Growth and Proliferation by the mTOR Pathway," *Protein Kinases and Protein Phosphorylation* FASEB Meeting, Snowmass, Colorado.

August 2005, "Signaling by the mTOR Pathway to Akt/PKB and S6K," *Glucose Transporter Biology* FASEB Meeting, Snowmass, Colorado.

August 2005, "Signaling by the mTOR Pathway to Akt/PKB and S6K," Research Seminar, Ariad Pharmaceuticals, Cambridge, Massachusetts.

October 2005, "Signaling by the mTOR Pathway to Akt/PKB and S6K," Research Seminar, Pfizer, Groton, Connecticut.

November 2005, "Signaling by the mTOR Pathway to Akt/PKB and S6K," Research Seminar, Cell Signaling Technology, Beverly, Massachusetts.

November 2005, "Signaling by the mTOR Pathway to Akt/PKB and S6K," Research Seminar, Praecis Pharmaceuticals, Waltham, Massachusetts.

January 2006, "New Approaches to the Study of Growth Control," Keystone Symposia titled "Signaling Networks", Vancouver, Canada.

February 2006, "mTOR Regulation of Growth and Proliferation," Pharmacology & Cancer Biology Signal Transduction Colloquium Seminar Series, Duke University.

March 2006, "Regulation on Growth by the mTOR Pathway," PTEN Pathways Conference, Cold Spring Harbor Laboratory, Cold Spring Harbor, NY.

April 2006, "New Approaches to the Study of Growth Control," Genome Sciences Departmental Seminar, University of Washington.

May 2006, "Regulation of Growth by the mTOR Pathway," Regina Elena Cancer Institute, Rome, Italy.

May 2006, "Signaling by the mTOR Pathway to Akt PKB and S6K," Second Annual IFOM-IEO Meeting on Cancer (The FIRC Institute of Molecular Oncology Foundation) and IEO (European Institute of Oncology), Milan, Italy.

May 2006, "Regulation of growth by the mTOR pathway," CNIO (Center for National Cancer Research) Conference on "PTEN and the AKT route", Madrid, Spain.

June 2006, "Regulation of growth by the mTOR pathway," Genentech, Corporation, San Francisco, California.

June 2006, "Regulation of growth by the mTOR pathway," 20th IUBMB International Congress of Biochemistry and Molecular Biology and 11th FAOBMB Congress. Osaka, Japan.

June 2006, Guest Lecturer Physiology, Marine Biology Laboratory, Woods Hole, Massachusetts.

July 2006, "Regulation of growth by the mTOR pathway," Gordon Research Conference on Molecular Cell Biology. Tilton, New Hampshire.

July 2006, "Regulation of growth by the mTOR pathway," Gordon Research Conference on Growth Factor Signaling. New London, Connecticut.

September 2006, "Lentiviral RNAi screening," Roche Pharmaceuticals, Nutley, New Jersey.

October 2006, "Regulation of Growth by the mTOR pathway," Max Planck Institute, Berlin, Germany.

October 2006, "Signaling through the mTORC1 and mTORC2 Pathways," Novartis Pharmaceuticals, Cambridge, Massachusetts.

January 2007, "Signaling through the mTORC1 and mTORC2 Pathways," 2007 Keystone Symposium on *Obesity: Peripheral and Central Pathways Regulating Energy Homeostasis*, Keystone Resort in Keystone, Colorado.

March 2007, "Signaling through the mTORC1 and mTORC2 Pathways," 2007 Pew Scholars Program in Biomedical Sciences. Puerto Vallarta, Mexico.

March 2007, "Signaling through the mTORC1 and mTORC2 Pathways," Cell Signaling Technology Seminar, Danvers, Massachusetts.

April 2007, "Signaling through the mTORC1 and mTORC2 Pathways," Pathology Department, Harvard Medical School.

May 2007, "Signaling through the mTORC1 and mTORC2 Pathways," New York Academy of Sciences Symposium: *The PI3K-PTEN-AKT-TOR Signaling Pathway in Cancer, Metabolism and Aging*, New York, NY.

May 2007, "Signaling through the mTORC1 and mTORC2 Pathways," Cell Biology Department, Johns Hopkins University School of Medicine.

May 2007, "Signaling through the mTORC1 and mTORC2 Pathways," Seminar Series, National Institute of Dental and Cranial Research, NIH.

June 2007, "Signaling through the mTORC1 and mTORC2 Pathways," Cancer Center Cell Biology Program Research Seminar Series, Memorial Sloan-Kettering, New York, NY.

June 2007, "Signaling through the mTORC1 and mTORC2 Pathways," Cantoblanco Workshop on Biology symposium titled "Signaling and Metabolic Pathways in Cancer", Madrid, Spain.

June 2007, "Signaling through the mTORC1 and mTORC2 Pathways," Beatson International Cancer Conference titled" Molecular Cancer Therapies: New Challenges and Horizons", Glasgow, Scotland.

June 2007, "Signaling through the mTORC1 and mTORC2 Pathways," Gordon Research Conference on Cell Proliferation titled " Molecular Therapeutics of Cancer", University of New England, Biddiford, Maine.

July 2007, "Signaling through the mTORC1 and mTORC2 Pathways," FASEB meeting on protein kinases titled "Protein Kinases and Protein Phosphyorylation", Indian Wells, CA.

July 2007, "Signaling through the mTORC1 and mTORC2 Pathways," Gordon Research Conference on Molecular Therapeutics of Cancer, New London, New Hampshire.

September 2007, "Metabolic Pathways in Cancer," Mahajani Symposium on Cancer and Metabolism, Salk Institute, La Jolla, CA.

September 2007, "mTOR and Disease," Tuberous Sclerosis Complex: From Genes to New Therapeutics Meeting, Annapolis, MD.

October 2007, "Signaling through the mTORC1 and mTORC2 Pathways," CNIO Spanish National Cancer Research Center Nature Symposium on Oncogenes and Human Cancer: The Next 25 Years, Madrid, Spain.

January 2008, "New Screening Technologies," 3V Biosciences Scientific Retreat, Menlo Park, CA

March 2008, "Nutrient Sensitive Growth Control by mTOR," Foundation IPSEN Annual Meeting titled "Metabolism and Cancer", Villa Caletas, Costa Rica.

March 2008, "Regulation of Growth by the mTOR Pathway," Beth Israel Deaconess Medical Center Endocrine Grand Rounds, Boston, MA.

March 2008, "Growth Control Through the mTOR Pathway," University of Pennsylvania Diabetes, Obesity & Metabolism Graduate Student Interest Group (IDOM) Seminar Series, Philadelphia, PA.

March 2008, "Regulation of Growth by the mTOR Pathway," Dundee Cell Signaling Lecture Series, University of Dundee, Dundee, Scotland, UK.

March 2008, "mTOR Signaling Pathways," Wyeth Research Frontiers in Human Diseases Symposium, New York, NY.

April 2008, "mTOR1 vs mTOR2," The LAM Foundation 2008 International Research Conference, Cincinnati, OH.

April 2008, "Growth Control by the mTOR Pathway," Weizmann Institute of Science, Life Science Colloquium Series at the Weizmann Institute, Rehovot, Israel.

May 2008, "RNAi Approaches to Growth Regulation," RNAi Mini Symposium, Taipei, Taiwan.

June 2008, "Signaling through the mTORC1 and mTORC2 Pathways," Gordon Research Conference on Protein Phosphorylation and G-Protein Signaling Networks entitled "Signaling Networks in Nutrient Sensing and Metabolism," University of New England, Biddeford, Maine.

July 2008, "Growth Control through the mTOR Pathway," Cell Signaling Technology, Danvers, Massachusetts.

July 2008, "New Approaches to Identify Cancer Targets," MPM Scientific Retreat, Endicott House, Dedham, Massachusetts.

November 2008, "Regulation of growth by the mTOR pathway," CNIO (Center for National Cancer Research) Conference on "Upstream of mTOR", Madrid, Spain.

November 2008, "Regulation of growth by the mTOR pathway," AACR Meeting on PI3K Signaling and Cancer", Cambridge, MA.

January 2009, "Large-scale Loss of Function Screens in Mammalian Cells," Keystone Meeting on "Omics Meets Cell Biology," Breckenridge, CO.

April 2009, "Growth Control by the mTOR pathway," Winter/Spring 2009 Pharmacology Seminar Course Series, Weill Cornell Medical College, New York, NY.

April 2009, "Growth Control by the mTOR pathway," Department of Cell Biology, Yale University School of Medicine, New Haven, CT.

April 2009, "Regulation of Growth by the mTOR pathway," 2009 Annual Meeting of the American Association for Cancer Research, Denver, CO.

April 2009, "Crosstalk between PI3K and mTOR," 2009 Keystone Symposia on PI 3-Kinase Signaling in Disease, Olympic Valley, CA.

May 2009, "Sizing up Caloric Restriction: Links to Cancer, Growth, & Aging," Whitehead Institute for Biomedical Research Young Professional Group (YPG) NYC Event, New York, NY.

June 2009, "The Therapeutic Potential of the mTOR Pathway," 21st Pezcoller Symposium, Unconventional Therapeutic Targets in Cancer, Trento, Italy.

June 2009, "Loss of function approaches in mammalian cells," Makota Life Sciences, Bedford, MA.

July 2009, "Amino acid sensing by mTOR," NCI/NINDS Cancer Cell Metabolism Workshop, Bethesda, MD.

July 2009, "Protein Kinases & Protein Phosphorlaytion," FASEB Summer Research Conference, Snowmass, CO.

Teaching

MIT Courses

Fall 2004, Course 7.22 "Development." Designed and taught one lecture in course developed by Hazel Sive and Ilaria Rebay.

Spring 2004, Course 7.16, "Biotechnology II (Project Lab)." Co-designed and co-taught entire course with Chris Burge.

Fall 2005, Course 7.20 "Human Physiology." Co-taught with Monty Krieger. Designed and taught second half of course.

Fall 2005, Course 7.22 "Development." Designed and taught one lecture in course developed by Hazel Sive.

Spring 2005, Course 7.16, "Biotechnology II (Project Lab)." Co-developed and co-taught entire course with Chris Burge.

Spring 2006, Course 7.16, "Biotechnology II (Project Lab)." Co-developed and co-taught entire course with Chris Burge.

Fall 2006, Course 7.20 "Human Physiology." Co-taught with Monty Krieger. Designed and taught second half of course.

Spring 2007, Course 7.16, "Biotechnology II (Project Lab)." Co-developed and co-taught entire course with Chris Burge.

Fall 2007, Course 7:50, "Molecular Biology: Methods and Logic." Co-taught with Leonard Guarente, David Houseman, Richard Hynes, Jackie Lees and Michael Hemann.

Fall 2008, Course 7:50, "Molecular Biology: Methods and Logic." Co-taught with Leonard Guarente, David Houseman, Richard Hynes, Jackie Lees and Michael Hemann.

Fall 2008, Course 7.20 "Human Physiology." Co-taught with Monty Krieger. Designed and taught second half of course.

Other Courses

Summer 2006, Physiology Course at Woods Hole Marine Biology Laboratory, Woods Hole, MA.
Spring 2008, "Nano Course on mTOR and Disease," Harvard Medical School, Boston, MA.

Postdoctoral Fellows and Associates Supervised

Anne E. Carpenter, Ph.D., Postdoctoral Fellow from 2002-2006. Currently she is the Director of the Imaging Platform at the Broad Institute, Cambridge, Massachusetts
Do-Hyung Kim, Ph.D., Postdoctoral Fellow from 2001-2004. Currently he is an Assistant Professor, Department of Biochemistry, Molecular Biology, and Biophysics at the University of Minnesota, Minneapolis, Minnesota
Jason Moffat, Ph.D., Postdoctoral Fellow from 2003-2007. Currently he is an Assistant Professor at the University of Toronto, Toronto, Canada
Tao Peng, Ph.D., Postdoctoral Associate from 1998-2003. Currently he is a Research Scientist, Center for Expression Arrays, Dept. of Microbiology, University of Washington, Seattle, Washington
Dos S. Sarbassov, Ph.D., Postdoctoral Fellow from 1999-2006. Currently he is an Assistant Professor at M.D. Anderson Cancer Center, Houston, Texas

Jacob Chudnovsky, Ph.D., Postdoctoral Fellow since 2006
Alejo Efeyan, Ph.D., Postdoctoral Associate since 2008
Brian Grabiner, Ph.D., Postdoctoral Associate since 2008
David A. Guertin, Ph.D., Postdoctoral Fellow since 2002
Nada Kalaany, Ph.D., Postdoctoral Associate since 2005
Seong Woo Kang, Ph.D., Postdoctoral Fellow since 2005
Mathieu Laplante, Ph.D., Postdoctoral Fellow since 2007
Dudley Lamming, Ph.D., Postdoctoral Fellow since 2008
Richard Possemato, Ph.D., Postdoctoral Associate since 2008
Jan Reiling, Ph.D., Postdoctoral Fellow since 2005
Yoav Shaul, P.D., Postdoctoral Fellow since 2007
Joon-Ho Sheen, Ph.D., Postdoctoral Fellow since 2002
Kris Wood, Ph.D. Postdoctoral Fellow since 2007
Roberto Zoncu, Postdoctoral Associate since 2008

Predoctoral Students Supervised

Siraj M. Ali, HST M.D./Ph.D student who completed his thesis in Spring 2005. Currently is a Pathology resident at BIDMC.
Maria (Xana) Frias, Graduate Assistant from 2003-2007. Currently is a post-doctoral fellow with Robert Darnell, Rockefeller University
Thouis Ray Jones, Computer Science Graduate Student (with Polina Golland) who completed thesis in Spring of 2007 and is currently at the Broad Institute
Carson Thoreen, MIT Biology Graduate Assistant since 2003-2008. Currently post-doctoral fellow jointly with lab of Nathanael Gray, DFCI.

Liron Bar-Peled, MIT Biology Graduate Assistant since 2008
Peggy Hsu, HST M.D./Ph.D student since 2006
Heather Keys, MIT Biology Graduate Assistant since 2007
Stephanie Kinkel, MIT Biology Graduate Assistant since 2008
Timothy Peterson, MIT Biology Graduate Assistant since 2004
Yasemin Sancak, MIT Biology Graduate Assistant since 2004
Shomit Sengupta, MIT Biology Graduate Assistant since 2004
Douglas Wheeler, Tri-institutional M.D./Ph.D student since 2008 (jointly with Charles Sawyers, MSKCC)

UROP Students Supervised

Alex Bagley, current M.D./Ph.D student, HST Program, Harvard and MIT
Andrew Markhard, Undergraduate Research Assistant and Summer Intern 2005 and 2006
Stephanie Oh, Undergraduate Research Assistant, 2008 - 2009
Jeff Meng, Summer Intern, Williams College, Summer 2009
Zhi Tsun, current MD/PhD student, HST Program, Harvard and MIT, Summer 2009

Committees

2003-present, Whitehead Institute Patent Committee
2003-present, Member of numerous thesis committees of MIT Biology Graduate Students
2004-present, Member of several thesis committees of Harvard Medical School Graduate Students
2004-present, Member of RNAi Platform Steering Committee at the Broad Institute
2005-present, Co-director with Michael Yaffe of the Cell Circuits Steering Committee at the Broad
2005-present, Member Broad Metabolism Group
Spring 2003, Member of MIT Biology Faculty Search Committee chaired by Robert Horvitz
Spring 2004, Member of MIT Biology Faculty Search Committee chaired by Robert Horvitz
Spring 2005, Member of MIT Biology Faculty Search Committee chaired by Robert Horvitz
Spring 2006, Member of Whitehead/MIT Biology Faculty Search Committee chaired by Hidde Ploegh,
Spring 2007, Member of MIT Center for Cancer Research Faculty Search chaired by Jackie Lees
Spring 2009, Member of MIT Center for Cancer Research Faculty Search chaired by Philip Sharp

Prelim Exam Committees (MIT)

Yasemin Sancak, Shomit Sengupta, Cindy Nielson, Gordon Lu, Ed Van Veen, Tamer Onder, Stacie Bumgarner, Brendan Kiburz, Sara Fenske, Tim Peterson, Kyle Farh, Giselle Roman, Mary Ellen Wiltrout, Brian Chin, Seraphim Thornton, Heather Keys, Peggy Hsu, Lina Bird

Thesis Advisory/Defense Committees (MIT)

Siraj Ali, Kuojung Lu, Sara Fenske, Tamar Onder, Kayvan Zainabadi, Piyush Gupta, Sarah Johnstone, Ji Luo, Neil Kumar, Drew Lowery, Seth Berman, Andreas Hochwagon, Honor Hsin, Ji Luo, Kevin Lai, Ray Jones, Oded Shaham, Joseph Kovac

Outside Thesis Advisory/Defense Committees

Joshua Baughman, Harvard University Medical School
Adam Friedman, Harvard University Medical School
Cory Johannessen, Harvard University Medical School
Nick Houstis, HST M.D./Ph.D.
Ji Lou, Harvard University Medical School
Aly Shamji, Harvard University
Scott Vafai, Harvard University Medical School
Jennifer Lee, Harvard University Medical School

Educational Commons

2004-2005, Reader of MIT Biology Graduate Student Application Folders
2005-present, Member of MIT Biology Undergraduate Teaching Committee chaired by Hazel Sive
2006-present, Member of MIT Biology Graduate Student Admissions Committee
2007, Organizer of Advisory Session for MIT Undergraduates applying to Medical School
2008, Organizer of Advisory Session for MIT Undergraduates applying to Medical School

2009, Organizer of Advisory Session for MIT Undergraduates applying to Medical School

Grant Reviewing

National Cancer Institute Program Project Reviewer 2002 and 2003

National Institute of General Medicine Program Project Reviewer 2003

National Cancer Institute Study Section Reviewer (Cell Signaling and Dynamics, CSD) 2006

National Cancer Institute, Cellular & Tissue Biology P01 Special Emphasis Panel 2009
National Institutes of Health, Challenge Grant Review, Panel 3, 2009

National Institutes of Health, Challenge Grant Review, Panel 6, 2009

Scientific Meetings Organized/Session Chair

May 2001, Fondation des Treilles: *TOR and the Control of Cell Growth*, Tourtour, France. Co-organized with Michael Hall, Biozentrum, Basel, Switzerland

December 2003, ASCB: *Cell Size/Shape Minisymposium*, San Francisco, CA. Co-organized with Judith Kimble, University of Wisconsin

April 2005, Keystone Meeting: *Systems and Biology*. Co- organized with Marc Vidal and Albert-Laszlo Barabasi

May 2005, Fondation des Treilles: *Cell Size and Shape*, Tourtour, France. Co-organized with Michael Hall, Biozentrum, Basel, Switzerland.

June 2008, Fondation des Treilles: Cell Growth and TOR Pathway", Les Treilles, France. Co-organized with Michael Hall, Biozentrum, Basel, Switzerland.

Peer Review of Manuscripts for:

BMC Cancer, Cancer Cell, Cancer Research, Cell, Cell Metabolism, Cell Stem Cell, Current Biology, Developmental Cell, EMBO, EMBO Reports, Genes & Development, Journal of Cell Biology, Journal of Physiology, Molecular Cell, Molecular and Cellular Biology, Molecular Pharmacology, PNAS, Nature, Nature Cell Biology, Nature Chemical Biology, Nature Genetics, Nature Medicine, Nature Methods, Nature Protocols, Nature Reviews Drug Discovery, Nucleic Acids Research, PLoS Biology, PLoS Medicine, Science, Science Signaling

Additional Professional Activities

2002-2004, Member of Scientific Advisory Board, Akceli, Inc.

2002-2005, Member of Scientific Advisory Board, Agencourt Biosciences, Inc.

2003, Member of Gene Expression Advisory Board, Wyeth/GI Research

2005-2008, Scientific Advisor for Cell Signaling Technologies

2004-present, Expert witness on the use of rapamycin in drug eluting stents, Johnson & Johnson

2007-present, Member of Scientific Advisory Board, Cellzome, Inc.

2008-present, Member of Scientific Advisory Board, Agios Pharmaceuticals, Inc.

2008-present, Member of Scientific Advisory Board, 3V Biosciences, Inc.

2009 – present, Member of Scientific Advisory Board, LabLife, Inc.